REMARKS/ARGUMENTS

Upon entry of the present amendment, claims 1-19 and 21-27 will be pending in this application and presented for examination. Claims 1, 7, 13 and 18 have been amended to more particularly point out and distinctly claims the subject matter Applicants regard as their invention. No new matter has been introduced with the foregoing amendments. Reconsideration is respectfully requested.

I. FORMALITIES

In the introductory comments, the Examiner inadvertently states that claim 19 was previously canceled. For the record, claim 20 was previously canceled, not claim 19. As such, claim 19 is currently pending and under examination.

II. CLAIM OBJECTIONS

Claims 7, 13 and 18 were objected to for various grammatical issues with regard to the English language translation of the Japanese specification. In response, Applicants have amended the claims as suggested by the Examiner. Accordingly, Applicants respectfully request that the objections to the claims be withdrawn.

The Examiner states that claim 8 does not further limit claim 7. Further, according to the Examiner, claim 14 does not further limit claim 12. In response, Applicants respectfully traverse the objections.

Claim 7 is drawn to interferon α and claim 8 further describes the sources of the interferon α, as either being natural interferon α, or interferon α made by recombinant methods. Claim 14 is similar to claim 8. As the Examiner is aware, under MPEP § 608.01(n):

> The test for a proper dependent claim under the fourth paragraph of 35 U.S.C. § 112 is whether the dependent claim includes every limitation of the claim from which it depends. The test is not one of whether the claims differ in scope.

Applicants are permitted to recite with greater particularity the source of interferon α, regardless of whether the specification recites that interferon α includes interferon α from natural sources and interferon α made by recombinant methods. As such, Applicants respectfully request that the Examiner withdraw the objection to the claims.

III. FIRST REJECTION UNDER 35 U.S.C. § 112

The Examiner rejected claims 1-19 under 35 U.S.C. § 112, first paragraph, as the specification is enabling for a mucosal adjuvant comprised of murine IFN α, but allegedly the specification is not enabling for the claimed composition wherein other sources of IFN α are used. In response, Applicants respectfully traverse the rejection.

As the Examiner is aware, the key to an enablement inquiry is whether undue experimentation is necessary for practicing the claimed invention. MPEP §2164.01. The invention as defined by the pending claims is a vaccine composition comprising a vaccine antigen and an interferon α, which composition induces both vaccine antigen-specific antibody in the blood and at the mucosal surface. The Examiner apparently takes the position that unless the composition is limited to the exemplary sources described in the specification, one of skill in the art would not know how to practice the invention. This position is legally untenable.

The present invention resides *inter alia*, in the discovery of the effectiveness of a vaccine composition comprising a vaccine antigen and an interferon α, which induces both vaccine antigen specific antibodies in the blood and at the mucosal surface. Applicants believe, and the Examiner agrees, that the specification is enabling for the claimed treatment composition wherein the IFN α is murine derived. However, Applicants contend that other sources of IFN α can be readily determined, identified and screened using methods that are either well known in the art or described in the specification. No undue experimentation is necessary.

The Examiner has offered specific reasons to support the enablement rejection. First, according to the Examiner, the breadth of the claims is excessive because the claims are drawn to a mucosal adjuvant that can comprise IFN α from any source. The Examiner states in part:

> The specification does not limit the type or source of IFN-a that can be used in the claimed mucosal adjuvant. The specification, on p. 6-7, discloses that various types of natural IFN-a produced by macrophages or leukocytes, recombinant IFN-a produced in various cell types, as consensus IFN-a can constitute the "family of several interferons a" that can be used commensurate in scope with the claims of the instant application. The specification, on p. 7, also states that "although there are no special restrictions", any IFN-a that is safe for use in humans can be used. It is well-known in the art that the family of proteins known as IFN-a has multiple subtypes, and that some of the different IFN-a subtypes exhibit differences in biological activity (citations omitted).

Second, according to the Examiner, undue experimentation on the part of the skilled artisan would be necessary to practice the invention. The Examiner states in part:

> ...the specification does not teach, or provide working examples of, any IFNa other than the murine IFN-a of Examples 1-2, that can be used as a mucosal adjuvant. Because of the potential differences in biological function of different IFN-a subtypes, a person of ordinary skill in the art would not be able to predict if every IFN-a subtype, produced in any type of host cell, could be used as a mucosal adjuvant as claimed.

Applicants respectfully *disagree* with the Examiner on these points.

First, as the Examiner has pointed out, the specification provides two working examples and 2 comparative examples to illustrate the claimed invention. In Example 1 on page 12, bridging to page 13, mouse nasal administration was performed in accordance with the literature reference method of Yamamoto *et al.* (S. Yamamoto *et al.*, *Proc. Natl. Acad. Sci. USA*, Vol. 94, 1997) using ovalbumin (OVA hereinafter). As recited in the specification, this antigen is widely used as a model antigen. Four or five C57BL mice per group were used and the interferon α was mouse interferon α, and it was administered at the same time as the antigen. After administration and subsequent challenges, blood was sampled 3 weeks, 4 weeks, and 6 weeks from the day of the initial administration. As described therein, the blood was centrifuged and the OVA-specific antibody titer in these serum samples (blood IgG) was assayed by the ELISA method (Table 1). As the results in Table 1 illustrate, the interferon α concomitant use group showed a significantly high OVA-specific blood IgG titer when compared to Comparative

Example 1 during all weeks. These results indicate that a systemic immune response can be effectively induced by nasal administration of vaccine concomitant with interferon α. Using the foregoing method as an model example, various other IFN α derived from other sources could be used to determine if a higher OVA-specific blood IgG titer is present in a vaccine composition of the present invention compared to a composition devoid of IFN α. The screening method described herein is routine.

Example 2 illustrates a similar experiment as Example 1, wherein, it is possible to use an ELISA method with fecal material. Moreover, in addition to the ELISA method described in detail in the specification, other methods such as high throughput screening systems using ELISA are known in the art (see, Mendoza LG *et al.*, *Biotechniques*. 1999 Oct;27(4):778-80, 782-6, entitled "High-throughput microarray-based enzyme-linked immunosorbent assay (ELISA)"). Using such methods, and *commercially available* TNF α from a variety of sources as well as those described in the literature, a skilled person would find it routine to identify and screen other TNF α from other sources. There are currently several commercially available recombinant interferon alpha preparations including, IFN-α2a (Roferon-A®, Hoffman-La Roche), IFN-α2b (Intron-A®, Schering-Plough), and IFN-α2c (Boehringer Ingelheim). The assays set forth in the specification are simple and can be automated. These assays can be used routinely to determine whether or not a selected IFN α can be used as taught and claimed.

In addition, the mice used in Examples 1 and 2 (i.e., the C57BL mouse) is the "gold standard" model in the interferon field. Consequently, the results are more convincing given the model used, and confirm the effect of INF α as a mucosal adjuvant.

Second, while it is true that the claims encompass a broad number of INF α, the literature is replete with their characteristic biological structure and function, as well as methods of isolation. Under the prevailing case law, routine screening of a potentially large number of candidate agents does not necessarily constitute undue experimentation. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 8 USPQ2d 1400,

1404 (Fed. Cir. 1988). In the present case, the experimentation is routine and a reasonable amount of guidance is given by the specification. Any necessary experimentation for practicing the claimed invention is therefore not "undue" under *Wands*. As such, it is established that no undue experimentation is necessary for practicing the claimed invention. In view of the foregoing, Applicants believe that the Examiner's specific concerns regarding the enablement issue have been fully addressed.

IV. SECOND REJECTION UNDER 35 U.S.C. § 112

Claims 1-19 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description support. In response, Applicants respectfully traverse the rejection.

The Examiner states:

> In this case, the only factor present in the claims is a requirement that the adjuvant comprise any IFN-a polypeptide, from any source or species. There is no identification of any particular subtype of IFN-a, other than the murine IFNa of Examples 1-2, which can function as claimed. Accordingly, in the absence of sufficient distinguishing characteristics, the specification does not provide adequate written description of the claimed genus of IFN-a polypeptides useful as an adjuvant.

Applicants assert that the claims fully comply with the requirements for written description of a genus as set forth in *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997). As described by the Federal Circuit in *Lilly*, "[a] description of a genus . . . may be achieved by means of . . . a recitation of structural features common to the members of the genus . . . ." *Lilly*, 43 USPQ2d at 1406. Furthermore, the court in *Fiers v. Revel* stated that an adequate written description "requires a precise definition, such as by structure, formula, chemical name, or physical properties." *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993).

As the Examiner has pointed out, there are a variety of known INF α subtypes and sources. However, as recited in Pestka article, (Pestka, *Biopolymers*, 2001, Vol. 55, p. 254-287 - see p. 260-261 Tables II), of the 14 human genes that comprise the IFN-α family, "*minor variants consisting of one or two amino acid differences account for the multiple alleles.*"

[Emphasis added]. In all likelihood, one or two amino acid differences will not make a difference with respect to a vaccine composition. As a result, the INF α family are defined via shared physical and structural properties.

> Moreover, as the Examiner is aware MPEP §2163 states:
>
> ....there may be situations where *one species* adequately supports *a genus*. See, e.g., *Rasmussen*, 650 F.2d at 1214, 211 USPQ at 32627 (disclosure of a single method of adheringly applying one layer to another was sufficient to support a generic claim to "adheringly applying" because one skilled in the art reading the specification would understand that it is unimportant how the layers are adhered, so long as they are adhered); *In re Herschler*, 591 F.2d 693, 697, 200 USPQ 711, 714 (CCPA 1979) (disclosure of corticosteroid in DMSO sufficient to support claims drawn to a method of using a mixture of a "physiologically active steroid" and DMSO because "use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds. Occasionally, a functional recitation of those known compounds in the specification may be sufficient as that description."); *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 285 (CCPA 1973) (the phrase "air or other gas which is inert to the liquid" was sufficient to support a claim to "inert fluid media" because the description of the properties and functions of the air or other gas segmentizing medium would suggest to a person skilled in the art that appellant's invention includes the use of "inert fluid" broadly.).

Therefore, Applicants believe that the instant specification appropriately describes the so-called IFN α "genus" using both structural and physical features, as required by the court in *University of California v. Eli Lilly*. In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the written description rejection under 35 U.S.C. § 112, first paragraph.

V. REJECTION UNDER 35 U.S.C. § 102(b)

The Examiner has rejected claims 1-2, 4-8, 10-14 and 16-19 under 35 U.S.C. § 102(b) as allegedly being anticipated by WO 00/20028 ("Staats *et al.*"). In response, Applicants respectfully traverse the rejection.

Under MPEP § 2131:

> [a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Staats *et al.* teach a method for eliciting an immune response against an antigen in a vertebrate by providing an antigen-adjuvant composition. Staats *et al.* teach the use of a substantially non-toxic adjuvant and exemplifies IL-1α and IL-1β. Further at the bottom of page 14, bridging to page 15 at the top, Staats *et al.* teach interleukins including:

> IL-1α, IL-1β, IL-2, IL-5, IL-6, IL-12, IL-15and IL-18; transforming growth factor beta (TGFβ); granulocyte macrophage colony stimulating factor (GM-CSF); interferon-gamma (IFNα); or other cytokine which has adjuvant activity.

Staats *et al.* teach a method wherein *interferon-gamma* is used. Apparently, Staats *et al.* has decided to define interferon-gamma as "IFNα" and not the traditional --IFNγ--. However, the current claims recite interferon alpha, wherein "IFNα" means interferon alpha and not interferon gamma. In any event, there is certainly no description of the effect of IFN α in Staats *et al.* As such, the claims are not anticipated by Staats *et al.*

VI. REJECTION UNDER 35 U.S.C. 103(a)

The Examiner has rejected claims 3, 9 and 15 under 35 U.S.C. § 103(a) as allegedly being obvious over WO 00/20028 ("Staats *et al.*"). In response, Applicants respectfully traverse the rejection.

No *Prima Facie* Case of Obviousness Exists

As set forth in M.P.E.P. § 2143:

> [t]o establish a *prima facie* case of obviousness, *three* basic criteria must be met. First, there must be some suggestion or motivation, either in the references

> themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

All three elements set forth above must be present in order to establish a *prima facie* case of obviousness. Applicants assert that a *prima facie* case of obviousness has not been established for the following reasons: 1) there is no suggestion or motivation to modify the reference; 2) there is no reasonable expectation of success; and 3) the cited art reference does not teach or suggest all the claim limitations.

There is No Suggestion or Motivation to Modify the Reference

Applicants state that there is simply no motivation or suggestion provided in the cited reference to modify its teaching in the way the Examiner has contemplated. Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Staats *et al.* provide a laundry list of various cytokines for example, IL-1α, IL-1β, IL-2, IL-5, IL-6, IL-12, IL-15and IL-18; transforming growth factor beta (TGFβ); granulocyte macrophage colony stimulating factor (GM-CSF); and interferon-gamma. These cytokines play a role in the differentiation and growth of T-cell and B-cell directly, and also in antigen-specific inducement of antibodies. In contrast, IFN α is secreted from macrophages and possesses an antivirus effect. For example, IFN α has antiviral activity on human AG-1732 and bovine MDKB cells Pestka article, (Pestka, *Biopolymers*, 2001, Vol. 55, p. 254-287 - see p. 262, column 1, under "Activities of the Purified INF-α Species"). As these are completely different

roles, there is simply no suggestion to use IFN α in view of the laundry list of Staats *et al.* As such, Applicants respectfully request that the Examiner withdraw the rejection.

The Cited Art References Do Not Teach All Limitations of the Claims

The prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). Applicants assert that the reference does not teach or suggest all the limitations of the claims and therefore, the obviousness rejection is untenable.

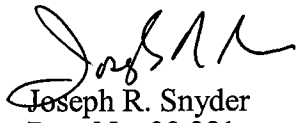
The Examiner has stated that Staats *et al.* do not teach the dose as is currently taught and claimed. However, as discuss above, Staats *et al.* teach a method wherein *interferon-gamma* is used. Apparently, Staats *et al.* has decided to define interferon-gamma as "IFN α" and not use the traditional Greek letter --γ--. The current claims are recite "IFN α." Further, Staats *et al.* do not teach the dose size as claimed.

As such, under *In re Wilson supra*, a *prima facie* case of obviousness has not been established because each limitation of the claims is not taught or suggested in the cited art references.

VII. CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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